Theoretical Study of the Effects of Amino Acids on One-electron Oxidation of a Nucleobase: Adenine Residue Can be a Hole-trapping Site

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Abstract

DNA damage by oxidative stress has been extensively investigated, but the effect of interaction with histone protein on the DNA oxidation has not been well-understood. The effects of amino acids on DNA oxidation induced by one-electron oxidants were examined by *ab initio* molecular orbital calculation at Hartree-Fock 6-31G* level. The calculated ionization potentials of nucleobases suggest that guanine is protected by interaction with amino acids from oxidative damage, whereas oxidation of adenine is enhanced through interaction with several kinds of amino acids. These findings suggest that adenine can be easily oxidized under the interaction with certain amino acid in chromatin rather than guanine, which can be most easily oxidized in isolated DNA. The effect of amino acids on DNA oxidation may explain the mutation at adenine residue induced by oxidative stress due to ultraviolet A irradiation.

Keywords: *Ab initio* molecular orbital calculation, Ionization potential, DNA damage, Amino acid, Oxidation

1 Introduction

DNA damage caused by one-electron oxidation of nucleobases has been extensively studied from the viewpoint of mutagenesis and carcinogenesis [1-5]. Since guanine is the most easily oxidized base among DNA nucleobases, the guanine radical cation is the initial product of DNA one-electron oxidation in a wide variety of isolated DNA systems [1-5]. The electron-loss center created in a DNA duplex by one-electron oxidation ultimately moves to end up at the hole-trapping site via hole migration through the DNA π -stack [2,5-8]. Various experimental [4,9-12] and theoretical [13,14] studies have revealed that GG, GGG, and GGGG sequences can be the hole-trapping site in the B-form DNA, leading to the formation of oxidative products of guanine. However, the approach to evaluate the genomic DNA damage has not been well established. Genomic DNA is packed into nucleosomes that further fold to form a higher-order chromatin structure. Therefore, the interaction between a nucleobase and an amino acid of a histone protein should play an important role in the oxidation of a nucleobase *in vivo* [15]. Indeed, oxidative DNA damage *in vivo* cannot be completely explained from the result of the study using isolated DNA systems [16,17]. In this study, the effect of an amino acid on DNA oxidation was examined using an *ab initio* molecular orbital (MO) calculation.

2 Methods

The *ab initio* MO calculations at the Hartree-Fock 6-31G* level were performed to elucidate the effect of amino acid on the ionization potential (*IP*) of nucleobases using Spartan 02' for Windows (Wavefunction Inc., CA, USA). The geometry of adenine-thymine (A-T) and guanine-cytosine (G-C) base pairs was constructed using Spartan 02' with standard B-form geometrical parameters optimized by the X-ray crystallographic analysis of relevant monomers and X-ray diffraction data of a polymer [18,19]. All the sugar backbones were replaced by methyl groups, keeping the position of all the atoms fixed. The equilibrium geometry of amino acid, which approaches the A-T or G-C base pair from the inter-planer direction, as shown in Fig. 1, was determined using molecular mechanics calculation. The geometry of base pairs was fixed during the calculation.

Figure 1 Scheme of the calculation model of the interaction between the nucleobase and the amino acid.

Table 1 Calculated *IP* (eV) of nucleobases associated with amino acids

	without interaction	Gly	Ala	Val	Leu	Pro	Tyr	Gln	Asp	Glu	Arg
A	8.02	7.84	7.82	8.12	8.11	8.45	7.97	7.76	7.86	7.93	7.45
		<i>-0.18</i>	<i>-0.20</i>	<i>+0.10</i>	<i>+0.09</i>	<i>+0.43</i>	<i>-0.05</i>	<i>-0.26</i>	<i>-0.16</i>	<i>-0.09</i>	<i>-0.57</i>
T	9.15	9.40	9.24	9.14	9.14	9.28	9.39	9.42	9.44	9.47	9.16
		<i>+0.25</i>	<i>+0.09</i>	<i>-0.01</i>	<i>-0.01</i>	<i>+0.13</i>	<i>+0.24</i>	<i>+0.27</i>	<i>+0.29</i>	<i>+0.32</i>	<i>+0.01</i>
G	7.21	7.51	7.47	7.46	7.63	7.47	7.77	7.71	7.83	7.61	7.68
		<i>+0.30</i>	<i>+0.26</i>	<i>+0.25</i>	<i>+0.42</i>	<i>+0.26</i>	<i>+0.56</i>	<i>+0.50</i>	<i>+0.62</i>	<i>+0.40</i>	<i>+0.47</i>
C	9.58	9.32	9.41	9.40	9.69	9.37	7.73	9.31	9.49	9.40	9.58
		<i>-0.26</i>	<i>-0.17</i>	<i>-0.18</i>	<i>+0.11</i>	<i>-0.21</i>	<i>+0.15</i>	<i>-0.27</i>	<i>-0.09</i>	<i>-0.18</i>	<i>±0.00</i>

The italics indicate the *IP* difference between the nucleobase associated with the amino acid and that without interaction.

3 Results and Discussion

The histone protein is commonly composed of the amino acids listed in Table 1 [20]. Table 1 shows the calculated *IP* of nucleobases associated with the amino acids. The *IP*s of adenine and guanine in all models are lower than those of thymine and cytosine, respectively, indicating that adenine or guanine can be the hole-trapping site in a DNA-amino acid system, rather than thymine and cytosine. The *IP* of guanine associated with each amino acid becomes larger than that without an amino acid, showing that the interaction with an amino acid results in protection of guanine from oxidation. On the other hand, the *IP* of adenine was lowered by the interaction with glycine, alanine, tyrosine, glutamine, asparagine, glutamic acid, and arginine, showing that the amino acid can enhance the oxidation of adenine. Especially, the *IP* of adenine associated with arginine is lower than that of guanine. The *IP* of adenine monotonically decreased with a shortening of the distance between nucleobase and arginine, whereas that of guanine increased (Fig. 2).

Figure 2 Calculated *IP*s of adenine and guanine interacted with arginine.

Although these calculations were based on the simplified model, the obtained results qualitatively demonstrated that the effect of interaction between adenine and arginine is quite different from that of guanine. The calculation of the equilibrium geometry of an intermolecular complex between base pairs and arginine showed their complexes through hydrogen bonding (Fig. 3). These calculations suggest that lowering the *IP* of adenine is due to the proton-donating character of the amino group of adenine through hydrogen bonding with the amino acid. Similarly, the increase of the *IP* of guanine should be due to the proton-accepting character of the carbonyl O and the N-7 of guanine in the hydrogen bonding with the amino acid. These results suggest that partly denatured site of DNA strand might be also a hole-trapping site through the interaction with amino acid.

Figure 3 Equilibrium geometry of intermolecular complexes between arginine and guanine or adenine.

In general, a guanine radical cation is finally formed through hole migration, when one-electron oxidation in isolated DNA is induced by an oxidant, such as a photoexcited photosensitizer. The present study has shown that the oxidation potential of an adenine residue may become lower than the neighboring guanine residues by interaction with a histone protein. Thus, a nucleobase radical cation formed in DNA may be finally localized on an adenine residue through hole migration or direct oxidation under certain conditions. Similarly to the reaction of a guanine radical cation [1,3], the formed adenine radical cation might react with a water molecule to form the C-8 OH adduct radical, followed by oxidation, leading to 8-oxo-7,8-dihydroadenine (8-oxo-A) [1]. An *ab initio* MO calculation has shown that 8-oxo-A forms a stable base pair with G (Fig. 4, formation enthalpy: $\Delta H = -12.0 \text{ kcal mol}^{-1}$), which is comparable to the Watson-Crick A-T base pair ($\Delta H = -10.7 \text{ kcal mol}^{-1}$) and may cause an A-T $\rightarrow$ C-G transversion.

UVA radiation induces DNA oxidation through Type I (electron transfer) and Type II (singlet oxygen) mechanisms by activation of various endogenous photosensitizers [1-5,10-12] because UVA is hardly absorbed by DNA. UVA frequently induces A-T $\rightarrow$ C-G transversion, rather than G-C $\rightarrow$ T-A and G-C $\rightarrow$ C-G transversions [16,17]. Thus, the oxidation of adenine associated with amino acids may play an important role in UVA-induced mutation. The mutation at adenine residue by UVA could not be explained from the experimental and theoretical studies using isolated DNA.

Figure 4 Calculated equilibrium geometry of a G : 8-oxo-A base pair.

4 Conclusions

In summary, this study suggests that adenine associated with a certain amino acid can be easily oxidized and is comparable to guanine in chromatin DNA. The lowering of *IP* of adenine is possibly due to the proton-donating character of the amino group of adenine through hydrogen bonding with the amino acid. UVA-induced mutation at adenine residue may be explained by the enhancement of oxidation of adenine by an interaction with the amino acid of histone protein.

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